3/9/05 10/509795

translation

PATENT COOPERATION TREATY

PCT/JP2003/006777

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 03018PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/JP2003/006777	International filing date (*day/month/year*) 29 May 2003 (29.05.2003)	Priority date (*day/month/year*) 31 May 2002 (31.05.2002)
International Patent Classification (IPC) or national classification and IPC C07D 231/56, 401/12, 403/12, 405/12, 409/12, 471/04, 495/04, 519/00, 471/08, 487/04, 401/06, 405/14, 409/06, 409/14, 403/04, 401/14, 413/14, 417/12, 413/12, 405/06, 403/06, 417/14, 413/04, 403/04, A61K31/416, 4162, 437, 439, 444, 422, 4196, 454, 496, 5377, 506, 497, 42, 4985, 4439, 4196, 4178, 4184, 427, 55, 454, 4245, 407, A61P21/00, 25/00, 14, 16, 28, 29/00, 37/06, 43/00		
Applicant EISAI CO., LTD.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 17 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 05 November 2003 (05.11.2003)	Date of completion of this report 11 May 2004 (11.05.2004)
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/JP2003/006777

I. Basis of the report

1. With regard to the elements of the international application:*

☒ the international application as originally filed

☐ the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the claims:
pages _____, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the drawings:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/JP2003/006777

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 59-61

because:

☒ the said international application, or the said claims Nos. 59-61 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

SEE SUPPLEMENTAL SHEET

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 59-61.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III.1

Claims 59-61 set forth inventions that pertain to methods for the treatment of the human body.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/JP2003/006777

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

SEE SUPPLEMENTAL SHEET

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. _____

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.3

The inventions set forth in claims 1-4 pertain to compounds represented by formula (I); the inventions set forth in claims 5-19 pertain to compounds represented by formula (II); and the inventions set forth in claims 20-23 pertain to compounds represented by formula (III) (additionally, claims 24-49 cite the compounds of the abovementioned three groups). The substituent groups for the general formulas are set forth alternatively; therefore, the scope of the general formulas includes an extremely large number of compounds. Therein, the only technical feature common to all of the abovementioned groups of compounds is the feature of having an indazole-like structure wherein a ring is further fused to the pyrazole ring.

However, it is well known that compounds having such a skeleton are useful in the treatment of various disorders (for example, refer to JP 4-247079 A and JP 2000-501105 A); therefore, the structure in question cannot serve to link the abovementioned groups of compounds and the production methods therefor so as to form a single general inventive concept.

In addition, the inventions set forth in claims 50-58 pertain to medicinal compositions that comprise the abovementioned compounds as active components. However, the actions of the compounds are disclosed in the abovementioned documents; therefore, this feature cannot serve to link the abovementioned groups of compounds and the production methods therefor so as to form a single general inventive concept.

Consequently, the abovementioned inventions do not fulfill the requirement of unity of invention.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.3

An investigation focusing on the compounds specifically set forth in the examples in the description of the present application showed that with regards to the structure of the ring that is fused to the pyrazole ring, the compounds set forth in the present application can be classified into at least four groups, comprising:

(1) compounds wherein a 5-member heterocyclic ring is fused to the pyrazole ring (a portion of the compounds represented by general formula (I) set forth in the claims);

(2) compounds wherein a 6-member heterocyclic ring comprising one nitrogen atom is fused to the pyrazole ring (a portion of the compounds represented by general formula (I) set forth in the claims and a portion of the compounds represented by general formula (II) set forth in the claims);

(3) compounds wherein a 6-member heterocyclic ring comprising two or more nitrogen atoms is fused to the pyrazole ring (a portion of the compounds represented by general formula (I) set forth in the claims and a portion of the compounds represented by general formula (II) set forth in the claims); and

(4) compounds wherein a benzene ring is fused to the pyrazole ring (the compounds represented by general formula (III) set forth in the claims). Therefore, the inventions set forth in claims 1-58 of the present application are considered to comprise four inventions corresponding to groups of compounds (1) to (4).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	51, 52, 54, 55, 58	YES
	Claims	1-50, 53, 56, 57	NO
Inventive step (IS)	Claims	51, 52, 54, 55, 58	YES
	Claims	1-50, 53, 56, 57	NO
Industrial applicability (IA)	Claims	1-58	YES
	Claims		NO

2. Citations and explanations

Document 1: EP 594001 A1 (Hoechst-Roussel Pharmaceuticals Inc.), 27 April 1994

Document 1 indicates that compounds represented by a general formula that overlaps with the general formulas set forth in the present application have an activity whereby they inhibit the re-uptake of serotonin.

Document 2: EP 239191 A1 (Beecham Group PLC), 30 September 1987

Document 2 indicates that compounds represented by a general formula that overlaps with the general formulas set forth in the present application have an anti-inflammatory activity.

Document 3: El-Taweel ABDEL-AZIZ et al., "Heterocyclic Amidines: Synthesis of New Azaindene Derivatives," Alexandria Journal of Pharmaceutical Sciences, 1998, 12(1), pages 11-15, retrieved from: Chemical Abstracts AN 129:81707 (online, retrieved on 28 July 2003)

Document 3 indicates compounds represented by RN:209343-84-0.

Document 4: S. A. S. GHOZLAN et al., "Nitriles in Organic Synthesis: Synthesis of Some New Polyfunctionally Substituted Pyrazines and Fused Pyrazines," Egyptian Journal of Pharmaceutical Sciences, 1992, 33(5-6), pages 859-867, retrieved from: Chemical Abstracts AN 121:35536 (online, retrieved on 28 July 2003)

Document 4 indicates compounds represented by RN:155779-11-6.

Document 5: Mohamed Gaber MAREI, "Preparation and Reactions of 6-aryl-1,5-dihydro-3-phenyl-4H-pyrazolo[4,3-c]pyridin-4-ones," Bulletin of the Chemical Society of Japan, 1993, 66(4), pages 1172-1175, retrieved from: Chemical Abstracts AN 119:139165 (online, retrieved on 28 July 2003)

Document 5 indicates compounds represented by RN:148116-47-6, RN: 148116-48-7 and the like.

Document 6: V. L. RUSINOV et al., "Nitro Azines. 20. Simple Syntheses of Pyrazolo-Condensed Nitropyridines from Aliphatic Nitro Synthons and Aminopyrazoles," Khimiya Geterotsiklicheskikh Soedinenii, 1992, 11, pages 1560-1564, retrieved from Chemical Abstracts AN 119:49293 (online, retrieved on 28 July 2003)

Document 6 indicates compounds represented by RN:98157-48-3.

Document 7: Mohamed Gaber MAREI, "Preparation and Reactions of pyrazolo[4,3-c]pyridin-4(5H)-ones," Afinidad, 1993, 50(443), pages 55-58, retrieved from Chemical Abstracts AN 119:28050

(online, retrieved on 28 July 2003)

Document 7 indicates compounds that are represented by RN:148116-47-6 and the like.

Document 8: JP 1-190681 A (Yoshitomi Seiyaku Kabushiki Kaisha), 31 July 1989

Document 8 discloses compounds represented by RN:65452-77-9 and RN:125035-41-8.

Document 9: R. RADINOV et al., "3-Phenylpyrazolo[4,3-c] pyridine and Derivatives: Structure Determination," Journal of Molecular Structure, 1987, 158, pages 99-108, retrieved from Chemical Abstracts AN 108:111448 (online, retrieved on 28 July 2003)

Document 9 indicates compounds represented by RN:113277-54-6.

Document 10: SU 1147712 A1 (Ural Polytechnic Institute, USSR), 30 March 1985, retrieved from Chemical Abstracts AN 103:123474 (online, retrieved on 28 July 2003)

Document 10 discloses compounds represented by RN:98157-48-3.

Document 11: L. CECCHI et al., "Synthesis of 1-N-glycosides of 3-Phenylpyrazolo[4,5-b] pyrazine," Farmaco, Edizione Scientifica, 1983, 38(1), pages 24-28, retrieved from Chemical Abstracts AN 98:143780 (online, retrieved on 28 July 2003)

Document 11 indicates compounds represented by RN:81198-03-0.

Document 12: L. CECCHI et al., "Reaction of 3-Phenyl-4,5-diaminopyrazole with 1,2-dioxo compounds 3-phenylpyrazolo[4,5-b]pyrazines," Farmaco, Edizione Scientifica, 1982, 37(2), pages 116-122, retrieved from Chemical Abstracts AN 96:142805 (online, retrieved on 28 July 2003)

Document 12 indicates compounds represented by RN:81198-03-0, RN:81198-04-1, RN:81198-05-2 and RN:81198-06-3.

Document 13: A. COSTANZO et al., "Synthesis of Some New Fluorine-Containing 5-amino-1,3-disubstituted Pyrazoles and 1H-pyrazolo[3,4-b]pyridines," Journal of Heterocyclic Chemistry, 1979, 16(6), pages 1141-1145, retrieved from Chemical Abstracts AN 92:146665 (online, retrieved on 28 July 2003)

Document 13 indicates compounds represented by RN:72411-60-0, RN:72411-62-2, RN:72411-69-9 and the like.

Document 14: M. KOCEVAR et al., "3-Diazopyrazolo[3,4-b]pyridine, a Versatile Synthon for New Heterocyclic Systems," Journal of Heterocyclic Chemistry, 1978, 15(7), pages 1175-1184, retrieved from Chemical Abstracts AN 90:22859 (online, retrieved on 28 July 2003)

Document 14 indicates compounds that are represented by RN:65452-77-9.

Document 15: EP 475352 A1 (Hoechst-Roussel Pharmaceuticals, Inc.), 18 March 1992

Document 15 indicates that compounds represented by a general formula that overlaps with the general formulas set forth in the present application can be used in relation to skin disorders.

Claims 1-49

The inventions set forth in claims 1-49 lack novelty and do not involve an inventive step in the light of documents 1-14 cited in the international search report, and document 15 or the like.

The present application sets forth compounds that are represented by general formulas (I) to (III); however, the extremely large number of compounds that are included within the scope of these general formulas are disclosed in documents 1-15. Furthermore, the following documents are indicated as being "X" category documents or "Y" category documents in relation to the inventions pertaining to the compounds set forth in the document PCT/JP02/03735 (WO 02/083648 A1), which was filed by the applicant of the present application and is considered to be closely related to claims 20-61 of the present application; therefore, these documents also suggest that the inventions set forth in the present application lack novelty and do not involve an inventive step.

Reference 1: WO 97/23480 A1 (The Dupont Merck Pharmaceutical Co.), 03 July 1997

Reference 2: WO 99/23077 A1 (Pfizer Products Inc.), 14 May 1999

Reference 3: JP 6-206872 A (Yoshitomi Seiyaku Kabushiki Kaisha), 26 July 1994

Reference 4: WO 00/21959 A1 (Janssen Pharmaceutica N. V.), 20 April 2000

Reference 5: EP 328200 A (Merck Sharp & Dohme Ltd.), 16 August 1989

Reference 6: M. PATEL et al., "Unsymmetrical Cyclic Ureas as HIV-1 Protease Inhibitors: Novel Biaryl Indazoles as P2/P2' Substituents," Bioorg. Med. Chem. Lett., September 1999, pages 3217-

3220, refer to the entire document

Reference 7: WO 97/03069 A1 (Glaxo Group Ltd.), 30 January 1997

Reference 8: WO 89/10924 A (National Research Development Corp.), 16 November 1989

Reference 9: EP 23633 A1 (Chugai Seiyaku Kabushiki Kaisha), 14 February 1981

Reference 10: JP 52-122366 A (Chugai Seiyaku Kabushiki Kaisha), 14 October 1977

Reference 11: JP 51-125281 A (Chugai Seiyaku Kabushiki Kaisha), 01 November 1976

Reference 12: DE 1266763 B2 (L. HORNER), 25 April 1968

Reference 13: W. D. JONES Jr. et al., "The reaction of 4-Alkyl-3-thio-semicarbazides with β-Haloketones," J. Heterocyclic Chem., 1983, 20, pages 1359-1361

Reference 14: H. KAWAKUBO et al., "3-aminoindazole Yuudoutai no Kouenshou, Chintsuu Oyobi Kanetsu Sayou," Yakugaku Zasshi, 1987, 107(1), pages 28-36

Reference 15: H KAWAKUBO et al., "Studies on 3-Aminoindazoles. I. Synthesis of 1- or 3-(Substituted 3-Amino)indazoles," Chem. Pharm. Bull., 1987, 35(6), pages 2292-2299

Reference 16: M. P. CAVA et al., "A Novel Pschorr Reaction in the Papaverine Series," J. Org. Chem., 1973, 38(13), pages 2394-2397

Reference 17: H. J. BOEHM et al., "Novel Inhibitors of DNA Gyrase:3D Structure Based Biased Needle Screening, Hit Validation by Biophysical Methods, and 3D Guided Optimization. A Promising Alternative to Random Screening," J. Med. Chem., 2000, 43, pages 2664-2674

Reference 18: Yasuo FUJIMURA et al., "2,3-Dihydro-1H-Pyrazolo[1,2-a]indazolium Yuudoutai no Gousei

to Yakuri Kassei ni tsuite," Yakugaku Zasshi, 1986, 106(11), pages 1002-1007, Chart 2

Reference 19: Yasuo FUJIMURA et al., "3-phenylindazole Yuudoutai no Gousei to Yakuri Kassei ni tsuite," Yakugaku Zasshi, 1986, 106(11), pages 995-1001

Claims 50, 53, 56 and 57

The inventions set forth in claims 50, 53, 56 and 57 lack novelty and do not involve an inventive step in the light of documents 1-14 cited in the international search report, and document 15 or the like.

The feature wherein compounds that fall within the scope of the compounds set forth in the present application can be used as medicinal drugs is disclosed in documents 1, 2 and 15, and the feature wherein these compounds have an anti-inflammatory action is disclosed in document 2.

Claims 51, 52, 54, 55 and 58

The inventions set forth in claims 51, 52, 54, 55 and 58 are novel and involve an inventive step in relation to documents 1-14 cited in the international search report, and document 15 or the like.

Documents 1-15 do not disclose or suggest a feature wherein the compounds set forth in the present application can be used as JNK inhibitors or can be used in the treatment, etc., of Alzheimer's disease.

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*

see supplemental sheet

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: VI.1

WO 02/083648 A1	24 October 2002	15 April 2002	16 April 2001
(Eisai Co., Ltd.)			
EX			

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The scope of the compounds represented by general formula (I) set forth in claim 1 comprises an extremely large number of compounds; however, only a few of the abovementioned compounds are disclosed in the sense of PCT Article 5 or are supported by the description in the sense of PCT Article 6.

Like the international search report, this international preliminary examination report was conducted in relation to the compounds that are specifically set forth in the description of the present application.